Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 6-8, 10, 15-17, 25, 26 and 36 are pending in the application. Claims 2-5, 9, 11-14, 18, 23, 24, 27 and 29-35 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1, 6, 7, 10, 15, 16, 25 and 36 are sought to be amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Election

Applicants note that on page 2 of the Office action, the Examiner stated that claims 23-27 and 29-35 are withdrawn from further consideration. The Examiner also stated that Group I (claims 1-18, 23-27 and 36) were elected for examination. Applicants note that Group I (claims 1-18, 23-27 and 36) were elected and thus, only claims 29-35 have been withdrawn from further consideration. Applicants respectfully request clarification in the next action from the U.S. Patent and Trademark Office.

Compliance with 35 U.S.C. § 120

The Examiner stated that Applicants have not complied with the conditions required to receive priority benefit under 35 U.S.C. § 120. Specifically, the Examiner stated that reference to the parent application was missing.

On page 1 of the Preliminary Amendment and Remarks filed February 29, 2001, Applicants added a section to the specification entitled "***Cross-Reference to Related Applications***" wherein the parent application was set forth. Thus, Applicants have complied with the requirements of 35 U.S.C. § 120.

Objection to the Disclosure

The Examiner objected to the Disclosure stating that the Brief Description of the Drawings is inserted incorrectly in the specification.

Applicants note that the *preferred* arrangement in framing the specification provides for the inclusion of the Brief Description of the Drawings between the Brief Summary of the Invention and the Detailed Description of the Invention. However, this arrangement is not required and, as Applicants have provided subtitles within the specification, it is clear where the Brief Description of the Drawings begins and ends.

Withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 23 and 25-27 under 35 U.S.C. § 102(b) as being anticipated by Everitt *et al.*, *Experimental Cell Research 199(1)*: 134-146 (March 1992). Applicants respectfully traverse the rejection.

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants canceled claims 23 and 27 and have amended claim 25.

The Examiner stated that Everitt *et al.* teach "expression vectors that express a transcript antisense to the SPARC [osteonectin] mRNA" as well as transfected cells.

To anticipate a claim, a reference must teach every element of that claim. Claim 25, as amended, recites a vector capable of transferring genetic material into a human cell, whereas Everitt *et al.* disclose transfection of mouse F9 embryonal carcinoma stem cells. Moreover, Claim 25, as amended, recites a vector that codes for an antisense polynucleotide that is able to bind to human osteonectin mRNA whereas Everitt *et al.* disclose a vector comprising a mouse osteonectin clone. The mouse clone is obtained as described by Mason *et al.*, *EMBO J. 5:* 1465-1472 (1986) (document AR7).

Since Everitt *et al.* do not disclose a vector capable of transferring genetic material into a human cell wherein the vector encodes an antisense polynucleotide that can bind to human osteonectin mRNA, Everitt *et al.* do not teach every claimed element and cannot anticipate claims 25 and 26.

Applicants assert that the rejection is in error and withdrawal thereof is respectfully requested.

The Examiner rejected claims 23 and 24 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,340,934. Applicants respectfully traverse the rejection.

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants canceled claims 23 and 24. Withdrawal of the rejection is requested.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected claims 1-18, 23-27 and 36 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office action, page 5). Applicants respectfully traverse the rejection.

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have limited the claims to compositions comprising antisense polynucleotide inhibitors of human osteonectin expression, vectors comprising the antisense polynucleotides and methods of use. Applicants reserve the right to file a continuation application directed to the broader embodiments described in the specification.

Applicants submit that antisense polynucleotide inhibitors of human osteonectin expression, vectors comprising the antisense polynucleotides and methods of use are fully described in the present application. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejected claims 1-18 and 36 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office action, page 8). Applicants respectfully traverse the rejection.

As discussed above, the claims have been limited to compositions comprising antisense polynucleotide inhibitors of human osteonectin expression, vectors comprising the

antisense polynucleotides and methods of use. Applicants submit that the present specification fully enables the practice of the claimed invention.

The Examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. A specification disclosure which contains a teaching of the manner and process of making and using an invention must be taken as as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is a reason to doubt the truth of the statements contained therein. See M.P.E.P. §2164.04. Applicants submit that the Examiner has not met this burden.

The Examiner has relied upon the publications by Stull *et al.*, Gerwicz *et al.*, Rojanasakul and Jen *et al.* in a effort to establish that there was scepticism towards the use of antisense polynucleotides as therapeutic agents. Applicants strongly disagree that these publications raise a reasonable doubt regarding the enablement of the present invention. Stull *et al.*, *Gerwitz et al.* and Rojanasakul (published 1995-1996) considered alone in no way represent the present state of the art. Although Jen *et al.* (published 2000) do discuss some difficulties with the delivery of antisense polynucleotides, Jen *et al.* also teach methods to improve delivery e.g. by administration together with cationic porphyrins, fusogenic peptides, and polyethylenimine. See page 314, col. 1.

Moreover, other publications support the enablement of the present invention. For example, Lewis *et al.*, *Proc. Natl. Acad. Sci (USA) 93*:3176-3181 (1996) (see accompanying Supplemental Information Disclosure Statement) describe a cytofectin, GS2888, which overcomes many of the shortcomings of the prior art cytofectins for delivering oligodeoxynucleotides and plasmids into cells. Lewis *et al.* state that GS2888 "offers the potential for its use in *in vivo* applications for both gene and antisense delivery and expands

the utility of antisense ODNs for their use in understanding gene function." See page 3176, col. 2, last sentence of first full paragraph. Thus, the teachings of Lewis *et al.* provide a reasonable expectation that tumour therapy with an antisense polynucleotide which binds to osteonectin will be successful.

U.S. 5,248,671 (see accompanying Supplemental Information Disclosure Statement) teaches a method for treating bone marrow cells with antisense RNA prior to reintroduction of the cells into an individual. The '671 patent also describes the use of antisense p53 oligonucleotides to inhibit proliferation of malignant cells *in vivo* (see col. 17). The '671 patent also teaches administration of the antisense oligonucleotides, e.g. as part of liposomes (see col. 17). Applicants note that issued patents are presumed valid under 35 U.S.C. §282. Thus, it must be presumed that the '671 patent enables the making and using of the claimed method of killing cancer cells with the recited antisense oligonucleotides. Consequently, the teachings of the '671 patent provide a reasonable expectation that tumour therapy with an antisense polynucleotide which binds to osteonectin will also be successful.

Other patents directed to therapeutic antisense polynucleotides that have issued, including polynucleotides useful for treating cancer, include U.S. Pat. Nos. 6,031,086, 5,457,189, 5,442,049, 6,238,921, 6,214,986, 6,190,869, 6,187,587, 6,187,585, 6,177,246, 6,171,860, 6,168,950, 6,165,791, 6,165,790, 6,165,789, 6,165,788, 6,165,786, 6,165,728, 6,159,734, 6,159,697, 6,159,694, 6,156,571, 6,153,595, 6,150,162, 6,140,126, 6,140,125, 6,140,124, 6,136,604, 6,136,603, 6,133,032, 6,133,031, 6,130,088, 6,121,047, 6,117,848, 6,117,847, 6,114,517, 6,030,837 and 6,030,786. See the Supplemental Information Disclosure Statement. In view of these many patents examined and issued by the U.S. Patent

and Trademark Office, it is clear that those of ordinary skill in the art would have no basis to doubt the enablement of the present invention.

Relying on Mercola *et al.* and Crystal, the Examiner has expressed doubt that antisense oligonucleotides can be delivered by an expression vector. Applicants submit that the Examiner's reliance on these 1995 publications is misplaced. As evidenced by the patents cited hereinabove and Lewis *et al.*, it is clear that methods for *in vivo* delivery of antisense polynucleotides for tumour suppression and treatment were well known before the present invention. Moreover, the present specification teaches particular methods of delivering antisense polynucleotides including, e.g. by direct injection into the tumour. See also, e.g. page 7, which teaches formulation of the polynucleotides in liposomes and direct injection into solid tumours.

Finally, it should be noted that down regulation of osteonectin expression completely prevented tumor formation in mice and induced a dominant "bystander" effect. See page 32, second full paragraph. This "bystander" effect provides that not all of the tumour cells need be transfected with the antisense polynucleotide.

In view of the state of the art as exemplified by Lewis *et al.* and the cited patents, when considered with Applicants' specification, it is clear that one of ordinary skill in the art would not doubt that the claimed invention is enabled. Accordingly, the rejection is in error and must be withdrawn. Withdrawal of the rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claims 2-5, 9, 11-14, 18, 23, 24 and 27 have been canceled.

Please substitute the following claim 1 for pending claim 1:

1. (twice amended) A pharmaceutical composition comprising an inhibitor of human osteonectin and a pharmaceutically acceptable carrier, wherein said inhibitor has an activity selected from the group consisting of: preventing expression of human osteonectin in tumour cells and decreasing expression of human osteonectin in tumour cells, and wherein said inhibitor comprises an antisense polynucleotide which binds to osteonectin mRNA so as to prevent or decrease expression of human osteonectin by preventing or decreasing translation of said mRNA into human osteonectin.

Please substitute the following claim 6 for pending claim 6:

6. (twice amended) The composition according to Claim 5, wherein said antisense polynucleotide is an antisense RNA complimentary to human osteonectin mRNA.

Please substitute the following claim 7 for pending claim 7:

7. (twice amended) The composition according to Claim [3] 1, wherein said inhibitor is conjugated to or administered in combination with a carrier molecule.

Please substitute the following claim 10 for pending claim 10:

10. (twice amended) A method of tumour therapy comprising administering to a patient in need thereof an effective amount of an inhibitor of human osteonectin, wherein said inhibitor has an activity selected from the group consisting of: preventing expression of human osteonectin in tumour cells and decreasing expression of human osteonectin in tumour cells, and wherein said inhibitor comprises an antisense polynucleotide which binds to osteonectin mRNA so as to prevent or decrease expression of human osteonectin by preventing or decreasing translation of said mRNA into human osteonectin.

Please substitute the following claim 15 for pending claim 15:

15. (twice amended) The method according to Claim [14] 10, wherein said antisense polynucleotide is an antisense RNA complimentary to human osteonectin mRNA.

Please substitute the following claim 16 for pending claim 16:

16. (twice amended) The method according to Claim [12] 15, wherein said inhibitor is conjugated to or administered in combination with a carrier molecule.

Please substitute the following claim 25 for pending claim 25:

25. (twice amended) A vector capable of transferring genetic material into a human cell, wherein said vector codes for an antisense polynucleotide which binds to human osteonectin mRNA and wherein expression of said [genetic material] vector results in a decrease or inhibition of osteonectin activity in the cell.

Please substitute the following claim 36 for pending claim 36:

36. (once amended) The method of Claim [1] 10, wherein the patient has cancer.